REVIEW

DIAGNOSIS ORIENTATION AND RISK STRATIFICATION IN SYNCOPE

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ABSTRACT

Syncope represents an important health issue due to the number of emergency room presentations as well as the costs associated either to patient evaluation, or to therapeutic means in certain situations. Despite recent endeavors to optimize the approach to a patient with syncope, this is still heterogeneous in day to day practice and inconsistencies with the current guidelines recommendations are still found. We use a case presentation of a cardiac syncope as a starting point in order to outline the initial evaluation and the serious adverse events risk stratification methods of a patient with syncope.

Key words: syncope, risk stratification, score, diagnosis

CASE PRESENTATION

A 62 years old female is referred to the cardiology department to undergo a tilt test as part of an evaluation for syncopal episodes. She describes the first episode 3 months earlier, during exposure to heat, while sitting down and bent over, without any prodrome. To date the patient does not have any known medical history. Upon arrival to the hospital she is evaluated using blood samples, an electrocardiogram (ECG), a 24 hour Holter monitor, an electroencephalogram (EEG) and a cerebral computed tomography (CT scan). Upon completion she is diagnosed with arterial hypertension and major left bundle branch block (LBBB). A therapy with perindoprilum and atorvastatin is initiated. Cerebral magnetic resonance imaging (MRI) is recommended. It has not revealed any abnormal findings. A carotid Doppler ultrasound describes hemodinamically insignificant atherosclerotic plaques. Two months later the patient experiences a new syncope, this time while walking, again without prodrome. In between the two syncope instances the patient describes several episodes of lightheadedness or feeling undefined malaise. She is evaluated once again by a neurologist and a cardiologist and a cerebral CT scan and a Holter monitor are obtained. The latter confirmed the LBBB and revealed ventricular premature beats. Consequently the patient is given sotalol. During her evaluation in our clinic she receives an orthostatic hypotension test, a carotid sinus massage, an echocardiogram and a tilt test which did not have any abnormal findings and the decision to stop sotalol is made. Subsequently a decision is made to implant a loop-recorder (ILR). Five months later upon analysis of the recorded data, two episodes of third degree atrioventricular blocks are found which coincide with the onset of symptoms described by the patient. As a result, the patient is implanted a dual-chamber pacemaker programmed for DDD pacing mode. A year after pacemaker implantation the patient was free of any syncope episodes. Some questions could arise from this case. Were all the tests performed in this case necessary as first investigations? When and how do we plan extensive evaluations or hospitalization of a syncope patient?

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INTRODUCTION

According to the latest European Society of Cardiology guidelines concerning the management of syncope[1], syncope is a transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery. The incidence of syncope varies depending on many factors such as age, sex and cause. Generally speaking there is a great variability regarding syncope incidence reports due to the population evaluated, the defining criteria used and the way in which the diagnosis is established. Retrospective studies on apparently healthy subjects show approximately 40% experience an episode of syncope (2,3). Other authors believe among 20 to 30 percent of the general population experience syncope at some point during their lifetime (4-6). The first epidemiologic study based on a cohort of the Framingham Heart Study finds a 3% incidence of at least one syncope among men and 3.5% among women (7) in the 5209 patient group followed over a period of 26 years, while Soteriades & al (8) found a 10% incidence rate inside a 7814 subjects lot recruited from the same Framingham Heart Study followed between 1971 and 1998 considering the fact that the latter was based on a larger definition of syncope, thus also including patients with epilepsy or transitory ischemic attacks. The incidence of syncope in the emergency department seems to be around 1% as the majority of reports show (9-13). The latest syncope classification divides this syndrome in three main categories: reflex syncope (vasovagal, situational, carotid sinus hypersensibility), syncope due to orthostatic hypotension (drug-induced, primary or secondary autonomic failure, volume depletion) and cardiac syncope (due to tachy- or bradycardia or certain structural diseases like aortic stenosis or obstructive hypertrophic cardiomyopathy). These possible causes for syncope differ by frequency of apparition as well as by the associated prognosis. The most frequent syncope is the reflex kind, followed by cardiac syncope, taking in consideration that the latter has a rising prevalence in the elderly population (8,14,15). When talking about prognosis the situation is reversed, a cardiac syncope associates a high mortality risk (HR: 2.01, IC95%: 1.48–2.73. $p < 0,001$), compared to the vasovagal kind (HR: 1.08, IC95%: 0.88–1.34, p = NS) (8). Hence the doctors' need to identify syncope patients with high risk of adverse events such as cardiac syncope patients is understandable, especially in the emergency department. Still, this task can prove to be very difficult especially in an emergency. Patients are generally stable and lack symptoms at the time they reach the hospital (16), more often than not the event lacks witnesses and the case history and anamnesis are often incomplete. This can lead to excessive hospitalizations that lack a clear benefit (17) while having a significant economical burden[18] and diagnostic errors. In the attempt to avoid all these while trying to have a consistent approach of a syncope patient, the current guidelines (1,19) are trying to implement a standardized and uniform approach (see Figure 1) which uses as a starting point a simple initial evaluation, easy enough to carry out even in an emergency department.

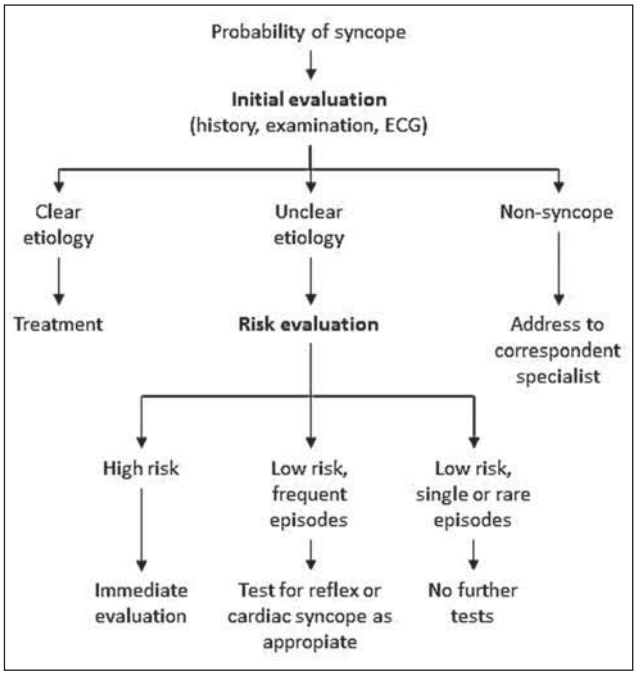

FIGURE 1. *Proposed algorithm for syncope evaluation. (adapted from) (1,19)*

INITIAL EVALUATION

The initial evaluation of a syncope patient consists of careful history, physical examination and electrocardiogram, after which 23 to 50% of cases have an etiologic classification of syncope (20,21). Diagnostic orientation and further management depend on a careful and thorough history taking. If the case history does not provide clues concerning the possible etiology of syncope, the chance for its subsequent establishment is minute, even after an extensive evaluation.

Important elements to look for in the case history (adapted after) (1,22) are:

- Prior circumstances: position (standing, sitting, and supine), activity (during or after ex-

ercise, changing position, urination, defecation etc.), predisposing or precipitating factors (crowded areas, heat, strong emotions, after a meal etc.).
- Prodromal: nausea, vomiting, sweating, abdominal discomfort, palpitations, blurred vision.
- Data about the attack (especially from the witnesses if there are any): way of falling, duration, breathing, involuntary movements (onset and duration), incontinence etc.
- Data concerning post-attack state: nausea, vomiting, drowsiness, neurological signs, trauma, chest pain, duration until recovery etc.
- Data about syncope personal history: age at onset, number of episodes, details about previous episodes.
- Personal and family history : family history of sudden death, cardiac and neurologic history, previous metabolic disease such as diabetes mellitus, drug or alcohol abuse, current and previous medication (a special attention should be for antihypertensive medication, psychiatric medication, antianginal medication, central nervous system inhibiting agents and drugs that QT-prolonging agents).

The clinical characteristics obtained during history taking are able to define the cause for syncope. Subsequently a reflex syncope is more probable among patients with a history of multiple syncope episodes, with nausea or vomiting as a prodrome, with trigger factors such as prolonged standing, exposure to heat, post-prandial period or after strenuous exercise. In contrast, cardiac syncope should be suspected when there is a family history of sudden death, when there is personal history of heart disease, when prodrome is in the form of palpitations or absent whatsoever, when syncope happens during exercise or a supine position or when the ECG is abnormal.

History taking should always be followed by a clinical examination that can identify situations such as orthostatic hypotension, dysautonomias, and the presence of heart disease or neurologic disease. The clinical examination starts by checking vital signs, such as blood pressure (BP) and pulse at arms, sitting and standing. Orthostatic hypotension is diagnosed when there is a drop of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure after 3 minutes of standing (23), but for it to be considered a cause for syncope repeating the initial symptoms is useful. A careful examination is needed regarding the cardiovascular system, especially for heart murmurs, both vascular and valvular, a blood pressure difference between arms, left ventricular dysfunction or pulmonary hypertension, the presence of gallop rhythm. Furthermore, the presence of cognitive or speech impairment, unequal blood pressure values between arms, motor or sensitive deficits, nystagmus, ataxia etc. can guide toward a neurological disease.

The electrocardiogram at rest completes the initial evaluation, it is often altered, approximately 50% of syncope cases (24), although an etiologic diagnosis is only met in 5% of cases (25). Even though it does not offer a certain cause of syncope the value of these findings is high due to the fact that it guides the physician toward a possible underlying cardiac disease and therefore toward specific tests that can objectify it. The most meaningful electrocardiographic findings are : inadequate sinus bradycardia (under 50 bpm. at any given moment), conduction disorders (sinoatrial block, bifascicular blocks etc.), QT interval changes, preexcitation, unsustained ventricular tachycardia (VT), repolarization changes suggestive for ischemia, changes suggestive for genetic disorders associated with arrhythmias (hypertrophic obstructive cardiomyopathy Brugada syndrome, arrhythmogenic right ventricular dysplasia). It is important to outline that a normal ECG does not rule out the possibility of a cardiac syncope due to the fact that up to 50% of patients over 40 years old without any significant underlying heart conditions experience an arrhythmia during syncope (26,27). This should not be a cause for abstaining from utilizing this test, the low cost and lack of any associated risk are pertinent arguments in favor of using the ECG at rest as a screening method for all syncope patients.

Occasionally blood tests can be useful in the initial evaluation of syncope, even though the so called standard blood test panels comprised of a complete blood count, blood glucose, creatinine, urea, electrolyte panel is rarely productive. In a study published by Linzer & colab. in 1997 (25) the presence of electrolyte imbalances, nitrogen retention or hypoglycemia was found in 2-3% of patients. In another report the complete blood count was diagnostic for hemorrhage as a cause for syncope in 5% of cases[4]. Most often this blood test is utilized for confirmation of a particular clinical suspicion rather than screening.

Should other tests such as cerebral imagery, carotid Doppler ultrasound or EEG be used routinely for these patients? The answer is no. The sole result is an augmentation in costs without any benefit whatsoever with the exception of appropriately selected cases after the initial evaluation.

Serious adverse events risk stratification

Frequently the initial evaluation does not yield an obvious diagnosis and the physician needs to hospitalize the patient for further evaluation. The main factor leading to hospitalization after syncope is the immediate or untimely risk of mortality. But hospitalization is usually not necessary even though it might seem reasonable from a forensic standpoint or to avoid major or minor complications. Even after hospitalization the cause may remain unidentified and the hypothesis that prognosis and recurrence rate are better has not yet been proved. Due to the fact that the highest costs are associated with hospitalization by default (28-30) several risk scores have been developed (see Table 1) in order to help physicians decide whether further evaluation or hospitalization in necessary, some evaluating short term risk, others long term risk.

Short term risk evaluation

Several trials have evaluated the short term risk of mortality or adverse events, usually defined under 30 days. Some of these trials have subsequently developed risk scores, two of which also have external validation studies.

TABLE 1. *Proposed scores for risk stratification in syncope. The results column represent the significance of diferent scoring system relative to endpoint or the specificity and sensibility in identifing the patients at risk of specified endpoint.*

Score	Points	Endpoint	Results
SFSR[31]			
Abnormal ECG History of congestive heart failure Hematocrit < 30% Systolic BP < 90 mmHg	0 : no risk ≥ 1: with risk	Serious adverse events at 7 days	Sensitivity: 96% Specificity: 62%
Syncope Risk Score[32]			
Age > 90 years Male sex History of arrhythmias Systolic BP >160 mmHg Abnormal ECG Abnormal troponin I Presyncope	+1 +1 +1 +1 +1 +1 -1	Serious adverse events at 30 days	Low (-1/0): 2.5% Intermediate (1-2): 6.3% High (3-6): 20%
ROSE[33]			
BNP ≥ 300 pg/ml Bradycardia ≤ 50 bpm prehospital or in emergency room Rectal exam. positive for hemorrhage Anemia (hemoglobine ≤ 90 g/l) Chest pain associated with syncope Q-waves on ECG (except in DIII) O2 saturation ≤ 94% in ambient air	0 : no risk ≥ 1: with risk	All-cause mortality and serious adverse events at 30 days	Sensitivity: 87.2% Specificity: 65.5% Negative predictive value: 98,5%
Martin & colab. (34)			
Age > 45 years Abnormal ECG History of ventricular arrhythmias History of congestive heart failure	1 for each	Mortality or severe arrhythmias at 1 year	Score 0: 0% Score 1: 5% Score 2: 16% Score ≥3: 27%
OESIL (35)			
Age > 65 years History of cardiovascular disease Absence of prodrome Abnormal ECG	1 for each	Mortality at 1 year	Score 0: 0% Score 1: 0.6% Score 2: 14% Score 3: 29% Score 4: 53%
EGSYS (36)			
Palpitations before syncope Abnormal ECG and/or cardiac disease Syncope in effort Syncope in supine Prodrome suggesting reflex mechanism (nausea, vomiting) Precipitants/predisposing factors	+4 +3 +3 +2 -1 -1	Risk of cardiac etiology	Score < 3: 2% Score 3: 13% Score 4: 33% Score >4: 77%

San Francisco Syncope Rule (SFSR)

In 2004 Quinn & colab. publish a prospective cohort study comprised of 684 patients with syncope or pre-syncope with the intention to find factors associated to serious adverse events at 7 days (mortality, myocardial infarction, arrhythmias, pulmonary embolism, ischemic stroke, subarachnoid hemorrhage, clinically significant hemorrhage or any other condition that would require a return to the emergency room or hospitalization). In the first report the score had a 96% sensitivity and 62% specificity (31). Later it was validated in another cohort comprised of 791 patients, showing similar sensitivity and specificity rates (37). Later it was validated in another cohort comprised of 791 patients, showing similar sensitivity and specificity rates (37). Consequent to validation there have been several analyses published that found 74% to 90% sensibility and 24 to 63% specificity, most drawing attention to the much lower specificity rates than in the validation lot (33,38-43). Furthermore, two of these external validation reports outline that the strict use of SFSR might lead to a rise in the number of hospitalizations (42,43).

Boston Syncope Rule

Grossman & colab. (44) have developed a clinical decision questionnaire (see Table 2) on the basis of the American College of Physicians' recommendations and the SFSR. The questionnaire was validated on a population of 362 patients with syncope, with the objective to outline any critical therapeutic intervention (PCI, pacemaker/defibrillator implantation, surgery, transfusion, resuscitation, changes in antiarrhythmic medication, interventional endoscopy, carotid stenosis interventional therapy) or adverse event (death, pulmonary embolism, tachyarrhythmias, hemorrhage, myocardial infarction, cardiac arrest, or severe consequences of syncope such as rabdomyolysis) that took place in the emergency room, during hospitalization or by the end of the 30 day surveillance period. Patients were considered at risk if any of the criteria included in the questionnaire was met. The reported results showed 97% sensibility, 62% specificity and 99% negative predictive value. According to the authors the use of this rule would reduce hospitalizations by 48%.

TABLE 2. *Boston Syncope Rule (adapted from) (44). AF – atrial fibrillation; ICD – implantable cardiodefibrillator; SVT – supraventricular tachycardia; VT – ventricular tachycardia; VF – ventricular fibrillation*

Main group	Variable
1. Signs and symptoms of acute coronary syndrome	Suggestive chest pain Ischemic ECG changes (ST elevation or depression ST) VT, VF, SVT, rapid AF, new ST-T changes Dyspnea
2. Significant cardiac history	History of coronary disease History of congestive heart failure History of VT/VF History of pacemaker History of ICD Use of antiarrhythmic drugs (except beta blockers or calcium channel blockers)
3. Family history of sudden death	1st degree relative with sudden death. Brugada syndrome, hypertrophic cardiomyopathy or long QT
4. Valvular disease	Heart murmur noted in history or on examination
5. Signs of conduction disease	Multiple syncopes in previous 6 months Rapid heartbeats reported by patient Syncope during exercise QT > 500 ms 2nd or 3rd degree AV bloc
6. Volume depletion	Gastrointestinal bleeding by hemoccult or history Hematocrit < 30 Dehydration not corrected in the emergency room
7. Persistence > 15 min of abnormal vital signs in the emergency room	Respiratory rate > 24 /min O_2 saturation < 90% Sinus rate < 50 bpm or > 100 bpm BP < 90 mmHg
8. Central nervous system	Primary event (i.e. stroke, subarahnoidian hemorrhage etc.)

Syncope Risk Score

Another useful score for adverse events risk evaluation is the *Syncope Rule Score* developed by Sun & colab (32). Its validation was carried out on a population of 2584 patients over the age of 60 showing 88% sensibility and 32% specificity. This score does not have any other validations that might confirm the initial results, same as the Boston Syncope Rule.

STePS Study

The *Short-Term Prognosis of Syncope* (StePS) (45) study was carried out between four emergency departments in the Milan region in Italy and it included 676 syncope patients. The immediate adverse events risk was evaluated at 10 days and it included cardiopulmonary resuscitation, pacemaker or defibrillator implantation, admittance to an intensive therapy unit and early rehospitalization. The multivariable analysis found the following independent risk factors: abnormal ECG, male gender, trauma and lack of prodrome.

ROSE Score

The *Risk Stratification of Syncope in the Emergency Department* (ROSE) study aimed to develop and validate a predictive clinical decision score for general mortality or severe adverse events at 30 days for patients with unexplained syncope. The independent variables were derived from the analysis of 550 patients found in the emergency department and later validated using another 550 patient cohort with an average age of 62.4 years (33). The decision to hospitalize was taken if any of the seven variables used in the ROSE score (see Tabel 1) was present. The validation study found 87.2% sensitivity, 65.5% specificity and 98.5% negative predictive value for the ROSE score. Among all variables BNP $\geq$ 300 pg/ml alone was predictive for 16 out of 39 severe adverse events or deaths of any cause (41%).

Long term risk evaluation

Most studies have evaluated the long term risk defined as mortality and/or adverse events at 1 year, except the EGSYS study which followed-up at 2 years.

Martin & colab.

Martin & colab. (34) attempted to find predictive factors for arrhythmias or mortality at 1 year in an initial lot of 252 syncope patients that were seen in the emergency room of a medical center in Pittsburgh. The factors they identified were abnormal ECG, history of ventricular arrhythmias or congestive heart failure and age over 45. The evaluation chart they used was later validated on a different population of 374 patients.

STePS Study

The STePS study found 6% mortality and 3.3% severe adverse events other than death after 1 year. The factors associated with this risk were: age over 65 and simultaneous neoplasm, cerebrovascular disease, structural heart disease, or ventricular arrhythmias (45).

The Osservatorio Epidemiologico sulla Sincope nel Lazio score (OESIL)

The OESIL score was developed on a population of 270 consecutive patients with a mean age of 59.5, presenting with syncope in six hospitals in the Lazio region, the aim being to identify mortality predictors after 12 months. The score and mortality rate found are available in Table 1 (35). This manner of approach was found to be 100% sensible and 22% specific in the validation group, while two other evaluations found 88-95% sensibility and 11-59% specificity (33,38).

EGSYS score

A team of Italian researchers published in 2008 a score meant for evaluating the risk of syncope with cardiac origin (36). The score was developed from a prospective analysis carried out on a group of 260 patients with syncope of uncertain cause and afterward validated on a different group of 256 patients. The mean follow-up time was 614 days. A score of ≥ 3 indicates a possibility of syncope with cardiac origin with 92% sensibility and 69% specificity as the researchers found in the validation group. Mortality in 1 years was found to be 2% for patients with a score of < 3 and 21% for patients that scored ≥ 3.

These risk scores are not perfect. Serrano & colab. published the first systematic review and metaanalysis in 2010 (46) of methodological quality and prognosis accuracy of different risk scores in patients with syncope presented to the emergency departments. Their analysis found that eight out of nine studies included had methodological inadequacies in the derivative study. Also, authors point out that only OESIL and SFSR scores were validated externally although results were inconsistent

between different studies due to variations in design and ECG interpretation.

Returning to our case we consider it represents a usual approach in clinical practice regarding a patient with syncope. The lack of history of syncope, the age of debut and the lack of prodromal symptoms did not suggest a common vaso-vagal cause. The repeated negative orthostatic challenge test invalidates a hypotensive cause. Also the absence of any history and signs for a neurological disease should retain the physician to evaluate such an etiology in the first place. Despite this the patient performed repeatedly extensive and unnecessary neurological examinations and tests. According to current european guidelines the apparition of syncope during effort, the sudden onset of loss of consciousness and the presence of LBBB on surface ECG are enough arguments to consider a cardiac etiology. Applying EGSYS score this patient had a score of 6 points which corespond to a 77% risk of having a cardiac syncope. In this regard the echocardiogram and Holter monitoring were correctly indicated. The next logical step in diagnostic algorithm was the implantation of an ILR which revealed the cause as mentioned.

CONCLUSIONS

Syncope remains a difficult issue for the physician regarding diagnostic approach and risk evaluation. In order to avoid the unnecessary costs through hospitalization or excessive tests, the risk for iatrogenic complications and diagnostic errors it is necessary to implement a standardized protocol of approach for syncope patients in accordance with the European syncope management guidelines. The protocol starts with an initial evaluation comprised of detailed history, physical examination and electrocardiogram and continues with risk stratification. To date neither one of the aforementioned scores has universal applicability. Whatever score is preferred it should be used alongside clinical judgment.

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